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U.S. Food & Drug Administration
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5630 Fishers Lane Room 1061
Rockville, MD 20857

Docket 2005D-0062
Novartis comments on Draft Guidance: FDA's "Drug Watch" for Emerging Drug Safety Information

August 4, 2005

Dear Sir/Madam:

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 81,400 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

As one of the world's largest pharmaceutical manufacturers, Novartis has committed extensive resources to the handling of safety information for its investigational and marketed products. The proposed Drug Watch has the potential to significantly impact our operations and we appreciate the opportunity to offer comments on this guideline.

General comments:

As stated in the Background section of the draft guidance, FDA has long provided information on drug benefits and risks to healthcare providers and patients. The proposed Drug Watch web page is a departure from the content, format, and timing of this information which, until now, has been made available when a) its significance became known, or b) it generated a specific concern, or c) it prompted regulatory action such as a labeling change. The proposed Drug Watch would make emerging drug safety information available to the healthcare community, patients and other stakeholders in a new format and earlier than in the past, while an issue is still under active review by the Agency and sponsor. Novartis supports transparency in establishing and communicating benefit and risk information to relevant stakeholders in an appropriate and timely manner. However, we have concerns regarding the potential unintended consequences of the proposed Drug Watch web page as described in the

draft guidance. Later in this document we will further illustrate this point through our experience with Elidel® (pimecrolimus), one of the first products subject to the posting of a Drug Watch Public Health Advisory.

- **Public health impact**: FDA should consider the public health consequences of Drug Watch information, a concern not addressed in the draft guidance. Summaries for drugs (e.g. pimecrolimus, tacrolimus) that have been posted in a predecessor format to the future Drug Watch page have focused exclusively on unquantified safety signals outside the context of potential benefits. This unbalanced presentation offers a distorted and alarming view of Drug Watch products to patients, who in some cases may stop medication on their own without consulting a physician. We believe there is a potential for frightening patients into making their own treatment decisions, an outcome that may have far greater impact on public health than an unsubstantiated signal. It is also important to consider the limited capabilities of many consumers to make informed decisions about managing their own care or deciding to seek professional advice. It is therefore critical to explain in detail not only the ambiguous nature of an emerging safety issue, but also the offsetting benefits of continued drug use, the comparative risks of discontinuing medication (either with or without a physician's consent), the range of possible treatment alternatives, and whether or not any specific actions by health care providers or patients are recommended.
- **Litigation impact**: Drug Watch may force clinicians to make treatment decisions not on medical grounds but over fear of being sued, thereby depriving patients of the most appropriate treatment for their conditions. Although postings are intended to be a "heads up" to health care professionals, in today's litigious medical environment it is almost certain that Drug Watch information will be used by plaintiffs' attorneys as "proof" of material safety risks, and that courts will allow the warnings as evidence of causation. A recent FDA Public Health Advisory for pimecrolimus and tacrolimus is reportedly a model for future Drug Watch updates. Despite the preliminary nature of the potential cancer risk described in the notification, several plaintiffs' attorneys have already established web sites for patient recruitment, citing the advisory as "proof" of a causal relationship. Juries are unlikely to appreciate the complex distinctions between a Drug Watch alert and other forms of regulatory action. In addition, plaintiffs' attorneys may make the argument that labeling was inadequate, despite the preliminary nature of the information and the absence of any required regulatory action. There needs to be very clear disclaimer language in the final guidance document, as well as on the Drug Watch web page.

  Fear of litigation could also lead to physicians practicing defensive medicine based on unvalidated safety signals, an outcome that is not necessarily in the best interest of patients. The ensuing publicity may also trigger a significant increase in poor-quality reports, particularly from consumers, which may obscure the rigor of the underlying signal.
- **Communication**: FDA needs to consider the global impact of public statements posted on its web site and should take measures to communicate the objectives and procedures for Drug Watch to international health authorities. The Agency is in many ways the *de facto* regulator for much of the world. Publicizing unvalidated safety signals is a new concept that, to our knowledge, has not been attempted outside the United States. Its acceptance and interpretation will vary widely in other

cultures. We believe the Agency should work closely with foreign health authorities so they can prepare themselves to handle local public responses to FDA Drug Watch postings.

- **Involvement of sponsors**: Sponsors should be consulted at the time FDA is conducting its initial analysis. They should also be given the opportunity to provide any additional information that may help clarify a signal and confirm its validity. Novartis believes that a minimum of 72 hours is required for sponsors to prepare for the announcement of any new safety information on the FDA web site. Preparatory activities include notifying international health authorities and local company offices, as well as preparing statements for response to questions from health care providers, patients, the media, and the financial community.
- **Need for clear, well-defined and consistently applied criteria for posting and removal of a drug**. The criteria for posting information on the Drug Watch web page need to be more explicitly defined. This is particularly important given that the information will be posted "before (FDA) has fully determined its significance". Given the risk of premature and/or inaccurate release of information that could lead to confusion or inappropriate actions by healthcare providers and patients, it is essential to have clearly-defined parameters for the selection of data to be posted, including strict quality control measures. Similarly, the section of the guidance document dealing with removing a product from the Drug Watch should provide more definitive criteria for removal and a description of how these criteria will be applied.

Section I (Introduction)

The document uses various terms such as "important emerging safety information", "early safety signals", "potential safety issues", "emerging risks", "potential safety risks", "drug risk information", and "significant emerging safety issues" interchangeably throughout the text. These terms are not synonymous, may not be well understood by those outside the drug safety community, and could potentially cause different levels of alarm. We recommend that the Agency choose one of these terms, define it clearly, and use it consistently, not only throughout the guidance document, but also in Drug Watch postings. To the extent possible, the definition should match that of an "important drug safety issue" as defined in FDA's *Manual of Policies and Procedures,* Section 4151-3. Novartis supports the term "important emerging safety information" as the best term to describe the nature of the information FDA intends to post on the Drug Watch website.

Section II (Background)

This section states that FDA's goal with the Drug Watch is to share emerging safety information before its significance has been fully determined "so that patients and healthcare professionals will have the most current information concerning potential risk and benefits of a marketed drug product upon which to make individual treatment choices." However, nowhere in the document is the appropriate inclusion of benefit information discussed. For patients and healthcare provider to make informed decisions, they must be given both risk and benefit information, as well as the comparative risk of discontinuing treatment and alternative treatment options. Novartis recommends that future Drug Watch postings also include information on the benefits of continuing drug treatment, the comparative risks of discontinuing treatment, and the range and benefits and risk of alternative available therapies.

Section IIIA (What information will be posted?):

- There is an inconsistency between the general inclusion criteria for Drug Watch (i.e. emerging safety issues) and the examples given in Section IIIA (specifically examples B and C). Both discuss "known" reactions to a theoretical drug rather than emerging safety risks, In addition, this section states that only "significant" emerging safety issues will be listed on the Drug Watch. Other parts of the document, however, claim the program is in part to determine if emerging issues are, in fact, significant at all. These contradictions generate uncertainties over the range of situations which FDA plans to include on the Drug Watch page. We also suggest that FDA not use the word "significant" in this context unless it is clearly defined.
- Presenting warning information on one single aspect of a drug in isolation may prevent consideration of the full set of warnings and precautions contained in the product's label and consideration of the approved indications, which are important to individual prescribing decisions. We suggest providing a link to the current package insert for the product so that physicians and other healthcare providers have ready access to the complete prescribing information.
- In the Introduction section of the draft guidance document, FDA states that it intends to work "as quickly as possible to assess and address the potential safety issues..." (lines 37-38. In addition, lines 130-131 indicate that FDA intends to update information on the Drug Watch frequently. We support these policies; however, the guidance document should include more information concerning a) the nature and frequency of the updating process, such as whether there will be a minimum cycle time for updating, b) what it will take to resolve an issue, and c) whether there will be an archive/history that shows the progress of emerging information over time. In addition, we suggest that all Drug Watch postings include information regarding the steps the Agency is taking to assess and address an emerging safety issue, and the estimated timeframe for completion of this assessment. Furthermore, since the drug sponsor possesses the most knowledge about a given drug and could provide additional information which may clarify or verify the potential signal, FDA should involve the sponsor in all aspects of posting information on the Drug Watch web site, including initial posting, updating, and removal.
- In addition to the disclaimer language described in the draft guidance, Novartis recommends that individual Drug Watch postings contain strongly-worded disclaimers in lay language to indicate that no relationship has been established between the emerging safety issue and the suspect drug, and that the information does not yet warrant labeling changes or other regulatory actions on the part of the manufacturer. A disclaimer acknowledging differences between the emerging issue and the label, and a hyperlink directing the reader to the approved prescribing information, should be included on the Drug Watch page.
- The guidance should also contain more specific information concerning the nature and frequency of the Drug Watch updating process. This is of particular importance for issues that may take long periods of time to resolve, in particular those involving very rare adverse events. We recommend there be a minimum interval for updating each posting, even if it is only to acknowledge that an emerging safety issue is still under review. In addition, we recommend FDA develop a version control process to

handle the potential confusion over new, updated, and outdated information. FDA should also consider dividing the Drug Watch web page into different sections that clearly distinguishes pending evaluations from completed ones.

Section IIIB (How will FDA decide which drugs will be included on the Drug Watch?):

- The criteria for adding drugs to the Drug Watch need to be more explicitly defined. This is particularly important because the information will be posted "before (FDA) has fully determined its significance" (line 65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers and patients, it is crucial to have clearly defined parameters for the selection of information to be posted, including meaningful quality control measures. Many of the criteria listed are vague and raise additional questions. For example:
    - Will the emerging safety issues be limited to serious AEs?
    - What is the strength of information required to make a determination that an emerging safety issue should be posted? What are the thresholds that will be used to determine credibility? (lines 167-168)
    - How will FDA determine whether the emerging safety issue is a class effect or not?
    - How will it be determined that an unapproved use of a product poses a significant risk to patients?

- Novartis strongly believes that the decision to add products to the Drug Watch should not come as a surprise to sponsors. It is appreciated that FDA may wish to act quickly and not engage in prolonged negotiations with industry. However, the Agency should at minimum provide sponsors with a short period of time (e.g. two weeks) in which to provide any supplementary information that may aid to further clarify the safety signal in question. These contributions may include, for example, new adverse events that are still in the processing cycle or knowledge of ongoing or unpublished company or private studies that may further substantiate or refute the issue.

- The draft guidance does not provide detailed information on who specifically will decide that products qualify for addition to Drug Watch. While the guidance infers that such decisions will be the duty of the complete and diverse membership of the Drug Safety Oversight Board, FDA's *Manual of Policies and Procedures*, Section 4151-3, indicates that posting decisions will be made by a subcommittee of six or fewer individuals. Novartis believes that assigning the authority to list products on the Drug Watch has serious, long-term ramifications for patients, prescribers, and industry, and therefore warrants the attention and expertise of the full board.

- There is no information provided on whether FDA intends to monitor the accuracy of its postings and evaluate the effects of the Drug Watch content on the behavior of healthcare providers and patients. Learning from these evaluations can help minimize "false positive" postings, limit inaccurate information, and improve processes related to risk communication.

Section IIIC (How will drugs be removed from the Drug Watch?)

- In order to bring closure to drug issues removed from the web page, it is important to create and maintain a permanent on-line reference to how each issue was addressed. Documenting resolution is an important aspect of the process that will ensure the public that Drug Watch entries haven't simply disappeared, thereby instilling greater confidence in the program.
- Novartis also advocates developing and publishing a more specific decision tree for removal (or de-activation) of Drug Watch listings. The current wording is highly subjective and gives little insight into what the removal criteria will be and how they would be applied. We further recommend setting a time interval (e.g. one year) for removing issues that have not or can not be resolved.
- Product removals should be publicized through the Agency's standard mechanisms for distributing safety information (e.g. press releases, MedWatch and CDER e-mail subscription services).

Section IIID (Will sponsors be notified that a drug will be placed on the Drug Watch?):

- Novartis believes it is insufficient to quantify the manufacturer notification time frame as "shortly". Delivering accurate information that has been properly validated is crucial to appropriate patient care and safety. It is, therefore, important that sponsors receive advanced notice of Drug Watch postings and adequate time to inform the agency of errors or misleading content (see "Unintended Consquences" on page 7 for examples from the Drug Watch entry for our product Elidel®).
- A great deal of preparation goes into corporate disclosure of new safety issues, especially for multi-national organizations. Groundwork typically includes mass communications to employees, sales forces, and other stakeholders. In addition, Medical and Safety departments must anticipate the spectrum of questions that media outlets, the financial community, and panicked customers will ask immediately following a Drug Watch announcement. They must ensure adequate resources are in place to deal with spikes in call volume and adverse event reporting. Health care professionals need to be prepared for the increase in calls they will receive from patients, and opinion leaders must be given advanced notice to deal with professional and media inquiries. In addition, local affiliate offices must translate Drug Watch information and be prepared to discuss it with their local regulators and customers. Presenting an intelligent and unified response benefits the image and credibility of sponsors and of the Agency. We encourage FDA to revise this section to recognize that it takes a minimum of 72 hours for companies to make even the most basic preparations for new safety announcements. That timeframe is contingent on the sponsor having complete and ongoing knowledge of the safety issue as it develops. This recommendation pertains to both initial and follow-up postings. Similar preparations for handling questions following a posting will be required by FDA internal staff.
- We are concerned with the notification process in the situation where FDA opts to list an entire class of medicines on the Drug Watch, as was the case recently in the Agency's decision to require black box warnings on all non-steroidal anti-inflammatory agents. Sponsors of most NSAIDs were unaware that cardiovascular and dermatologic reactions were "emerging safety issues" for their products. Most were put in the awkward position of explaining the new warnings and their lack of supporting evidence to international health authorities, healthcare providers, and patients. FDA should provide timely and sufficient information and documentation to

sponsors of all products in the affected class so that they can adequately explain the situation to all their customers.

Section IIIE (How will the Drug Watch affect the promotion of prescription drugs?)
We agree with the position outlined in the draft guidance that information posted on the Drug Watch Web site should not be used for promotional purposes, and suggest that the guidance document include a specific statement that information on the Drug Watch that is not also mentioned in the label is "off limits" for promotional purposes, since it is preliminary in nature. This would also include counter-detailing.

Unintended Consequences

Given that the first Public Health Advisory was published on one of Novartis' products, Elidel® (pimecrolimus), we are in a unique position to provide feedback on our experience following the Public Health Advisory and Talk Paper postings on the FDA web site:

- **Posting of incorrect and misleading information by FDA in the Pubic Health Advisory and FDA Talk Paper**
  There are numerous examples of incorrect and misleading information contained in the March 10, 2005 FDA website posting.
  1) Both the FDA Public Health Advisory and FDA Talk Paper state it has already been established that a black box warning will be added for Elidel. At the time of the posting (and as of the date of this communication), this was not correct information.
  2) There is also no acknowledgment of expert opinions presented at the Pediatric Advisory committee that the types of lymphomas seen in Elidel patients n the postmarketing reports are not immunosuppression-related.
  3) Postmarketing reports of cancer are not balanced with reports of malignancies from clinical trials, which included reports from the vehicle/control arm (which were more frequent than in the active arm).
  4) The fact that animal model doses were at least 17X higher than the Maximum Recommended Human Dose for Elidel Cream is not stated. The Talk Paper also makes no distinction about the different dosage forms and routes of administration used in the specific animal studies, and the Public Health Advisory implies that the marketed product was used in all cases, when in fact oral pimecrolimus or pimecrolimus dissolved in ethanolic solution were also used.
  5) The FDA Talk Paper states that Elidel is "applied to the skin to control eczema by suppressing the immune system"; there is no indication that the drug's effect on eczema is based on systemic immunosuppression.

- **Misreporting and misrepresentation of the information on the FDA website by the medical community and media**
  Incorrect or out-of-context information can be amplified and widely disseminated by the media. This misinforms clinicians and potentially leads to inappropriate treatment of patients. The Mayo Clinic, Pharmalive.com, *Skin and Allergy News, Pediatric News,* and *Internal Medicine News*, American Academy of Dermatology, as well as the general news media (e.g. Associated Press, Reuters, Dow Jones, MSNBC) are examples of misreporting and misrepresentation of the FDA communication. The Mayo Clinic website stated that Elidel already had a "black box" warning and suggested that the preclinical animal studies revealed a connection

between Elidel and cancer. Mayo Clinic later revised its initial statement: "Research shows the creams are absorbed into the body and can cause cancer." *Pediatric News* and the July *Presidential Update from the American Academy of Dermatology* incorrectly stated that Elidel had received a "black box" warning, and the news services suggested that Elidel causes cancer and discuss the animal data as if they were proof of a connection. However, no explanation was presented regarding how divergent the doses were in the animal versus human studies, or that most of these data were available when the FDA approved Elidel. On an international level, *Scrip*, the European version of the *Pink Sheet*, stated on two occasions that a boxed warning had been implemented for Elidel. The investment community experienced similar confusion and misunderstanding of the information on the FDA website. If Novartis had had the opportunity to comment on the Drug Watch posting before its release, much of this confusion could have been avoided.

- **Undermining of the relationship between International Health Authorities and the local Novartis companies**
  Various international Health Authorities contacted their local Novartis office and questioned why they had learned about these important label "changes" from the FDA website and not directly from the sponsor. Misimpressions and misinformation have global consequences that can be magnified when foreign health authorities are forced to respond to their constituents with incomplete or unbalanced safety warnings.

- **Significant negative and widespread impact on both physicians treating and patients suffering from eczema**
  One of the most serious and distressing consequences is that non-medical concerns are dictating many eczema treatment decisions. Our survey of 300 treating physicians found that the majority of therapeutic changes by practitioners were not based on concerns related to the supposed risk of lymphoma or infections, but that treatment changes were driven by concern of potential legal liability, needing to invest too much time to inform or address the concerns of patients or parents requesting to switch treatment due to fear, and managed care organizations encouraging switches in patients' medication. In addition, when 20 eczema experts specializing in pediatric dermatology, dermatology and pediatrics were interviewed one-on-one, they expressed concern that physicians may now over treat their patients with steroids—which have significant well-established toxicity—or under treat them due to inaccurate information or misrepresentation of risk.

- **Negative impact on public health due to shift in treatment**
  Pediatricians have expressed concern that due to unwarranted fears, patients or their parents may make inappropriate decisions abut their treatment, including delay of treatment or reduced compliance. The result is worsening of patients' disease states, frustration with the lack treatment options perceived to be safe, and the loss of trust in their doctors. In some cases, cancer screenings are being requested. Cost of care could also be impacted. Forty-two per cent of survey physicians who reported they will switch patients from topical calcineurin inhibitors (TCIs) to steroids said they will increase patient office visits to monitor for side effects of steroids. They also indicated they would prescribe therapy for shorter periods of time with fewer refills. Overall, this will result in a increased burden for patients and their parents with a corresponding increase in costs. In addition, a number of case reports from

nationally renowned pediatric dermatologists demonstrate the need for costly rescue treatments, e.g. oral corticosteroids, antibiotics, oral cyclosporin A, hospitalizations, from severe exacerbations of atopic dermatitis in patients previously well-controlled on TCIs and occasional mid-potency topical corticosteroids.

We hope this feedback is of value in finalizing the draft Drug Watch guidance. Thank you very much for giving us the opportunity to comment.

Sincerely,

THOMAS UMRATH FOR

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